

# ALIEN PROPERTY CUSTODIAN

## MEDICAMENTS AND PROCESS FOR THE MANUFACTURE THEREOF

Emil Eidebenz, Wiesbaden-Biebrich, Germany;  
vested in the Alien Property Custodian

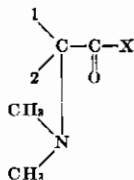
No Drawing. Application filed December 7, 1936

This invention relates to a process for the manufacture of agents acting as local anaesthetics and on the blood pressure.

Ephedrine and its hitherto known derivatives possess, apart from their action of increasing the blood pressure, no therapeutically utilisable action as local anaesthetics.

It has now been found in accordance with the present invention, that by modifying the ephedrine molecule substances having a therapeutically utilisable action as local anaesthetics are obtained without at the same time losing the action of increasing the blood pressure.

In accordance with the invention the originating materials treated are bodies of the following constitution:



in which 1 and 2 are alkyl or hydrogen and X aryl, amino or oxyalkyl. The aforesaid substances are subjected in accordance with the invention to the Grignard reaction, namely with aryl Grignard solutions. The originating products are thereby converted into substances which contain, in addition to a tertiary OH group, a double aryl group attached to the carbonyl-carbon atom.

A particularly good yield of the desired agents having the action of local anaesthetics and of increasing the blood pressure is obtained if the Grignard reaction be not carried out as generally usual with equimolecular quantities of Grignard reagent, but if an excess of the Grignard compound be present in the conversion. In general good yields are obtained by employing two molecules of the Grignard reagent, for example when subjecting an amino-ketone to the Grignard reaction, and by employing three molecules of the Grignard reagent when subjecting an amino-acid ester to the Grignard reaction.

The following embodiments of the process given by way of example describe the subjecting to the Grignard reaction of a ketone in which the X corresponds to an aryl group, and the subjecting to the Grignard reaction of an ester in which in the foregoing formula the X corresponds to an oxyalkyl group.

### EXAMPLE I

A Grignard solution is prepared in known manner from 6.4 magnesium, 40 grams benzene bromide and 100 ccm. absolute ether and 20 grams of dimethylamino-acetophenone, dissolved in 50 ccm. of absolute ether, are added drop by drop thereto. The reaction, which takes place violently at first, is concluded by heating for from 1 to 2 hours on the water bath. The reaction product is poured onto ice and treated with concentrated hydrochloric acid until it is acid to Congo Red. The hydrochloride of diphenyldimethylamino-methylcarbinol precipitated in this process is purified either by recrystallisation from water or by dissolving in and precipitating with acetone from methyl alcohol. The yield amounts to from 70% to 80% of theory.

### Properties

The hydrochloride is obtained in the form of white plates by precipitation from alcohol with ether. It is readily soluble in water and alcohol, fairly sparingly soluble in acetone and insoluble in ether. Melting point=230-232° C. with decomposition. The base, after recrystallisation from 50% alcohol, has a melting point of 55° C. It is readily soluble in alcohol, ether, benzene, chloroform, petroleum ether and insoluble in water.

### EXAMPLE II

A mixture of 15 grams of dimethylglycine ester and 100 ccm. of absolute ether is added drop by drop to a Grignard solution of 9.6 grams of magnesium, 60 grams of benzene bromide and 200 ccm. of absolute ether. The reaction which proceeds with sputtering and boiling, is kept within moderate limits by cooling. The product is worked up in the manner set forth in Example I.

When using the dimethylamino acid amides as originating materials the process can best be carried out in two stages. By treating the dimethylamino acid amides with arylmagnesium halides the former are first converted into aromatic aminoketones, which are then converted in turn into the corresponding amino-alcohols by further treatment with arylmagnesium halides.

### EXAMPLE III

A solution of 20 grams of dimethyl-amino-acetic acid dimethylamide in 50 ccm. of absolute ether is added drop by drop to a Grignard solution of 72.5 grams of benzene bromide, 11.2 grams of magnesium and 200 ccm. of absolute ether. By heating for two hours on the water bath the

reaction is completed and the reaction product is treated with ice and hydrochloric acid. The base precipitated with ammonia is dissolved in ether, dried with calcium chloride and distilled in vacuo. A yield of approximately 80% of pure dimethylaminoacetophenone is obtained. The amino-ketone thus obtained is converted into diphenyldimethylaminomethylcarbinol in the manner set forth in Example I.

## EXAMPLE IV

*Dimethylaminoacetophenone from dimethylaminodiethylacetamide*

A Grignard solution is prepared from 150 grams of brom-benzene, 23 grams mg and 400 ccm. of absolute ether and to it are added 60 grams of dimethylaminodiethylacetamide in 200 ccm. of ether. After heating for one hour on the water bath the product of reaction is treated with ice and hydrochloric acid, the base precipitated with ammonia, dissolved in ether and distilled in vacuo after the removal of the ether. Yield 46 grams of dimethylaminoacetophenone=74% of theory.

## EXAMPLE V

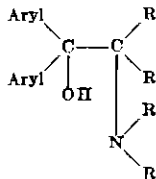
*Dimethylaminomethyl-1,3-dimethylphenylketone*

40 grams of dimethylaminodimethylacetamide in 150 ccm. of absolute ether are added to a Grignard solution made from 150 grams of 1,3-dimethyl-4-brom-benzene, 20 grams of magnesium and 400 ccm. of absolute ether. The reaction is completed by heating for from 2 to 3 hours on the water bath. The dimethylamino-1,3-dimethylphenylketone precipitated with the aid of ammonia from the reaction product treated with ice and hydrochloric acid, is dissolved in ether and after drying with potash is distilled in vacuo. Boiling point (11-13 mms. Hg)=144-146° C. The yield amounts to from 60% to 65% of theory.

## EXAMPLE VI

*α-dimethylaminopropiophenone*

A Grignard solution of 80 grams of brom-benzene, 12.4 grams of magnesium and 200 ccm. of absolute ether is made to react with a solution of 30 grams of α-dimethylaminodimethylpropionamide in 100 ccm. of absolute ether. The reaction product obtained after heating for two hours on the water bath yields after treatment with ice and hydrochloric acid and precipitation with ammonia 26 grams of α-dimethylaminopropiophenone=70% of theory. The compounds described in the foregoing become of particular therapeutical value when they possess the following constitution:



wherein R is H or alkyl and one or both aryl groups contain at least 8 carbon atoms. These substances however, possess no action on the blood pressure or practically no such action, while their surface anaesthetic and bactericidal properties are increased many times. It is surprising and completely unexpected that despite the in-

crease in the bactericidal power the toxicity towards warm-blooded animals is considerably smaller.

Compounds of this kind are obtained by causing the corresponding arylmagnesium compounds to react with amino-acid esters or aryl-aminoalkylketones in the manner similar to that described in the foregoing.

## EXAMPLE VII

*Bis-(1,4-dimethylphenyl)-dimethylaminomethylcarbinol*

A Grignard solution is prepared in the customary manner from 130 grams 2-brom-p-xylene, 17 grams magnesium and 300 ccm. absolute ether and to this solution 30 grams of ethyl dimethylamino acetate in 50 ccm. of ether are added gradually with stirring. The reaction is completed by heating for several hours under reflux, and the reaction product is treated with a little ice and hydrochloric acid. After standing for several hours the bis-(1,4-dimethylphenyl)-dimethylaminomethylcarbinol hydrochloride crystallises quantitatively from the concentrated magnesium chloride lye and is purified by recrystallisation from water.

## EXAMPLE VIII

*Bis-(1,3-dimethylphenyl)-dimethylaminomethylcarbinol*

A solution of 30 grams dimethylglycine ester in 50 ccm. ether is added drop by drop to a Grignard solution of 90 grams 1,3-dimethyl from benzene, 11.5 grams magnesium and 250 ccm. ether, and the mixture is heated for several more hours under reflux until the reaction is completed. The solution is treated with ice and hydrochloric acid and worked up in a similar manner to that set forth in Example VII.

## EXAMPLE IX

*Bis-(1,2-dimethylphenyl)-dimethylaminomethylcarbinol*

30 grams dimethylamino-ethyl acetate in 50 ccm. absolute ether are dropped while shaking into a Grignard solution of 120 grams 1,2-dimethyl-4-brom-xylene, 15.5 grams magnesium and 300 ccm. absolute ether. After heating for from two to three hours under reflux the reaction product is poured on to ice and the basic magnesium bromide precipitated is treated with hydrochloric acid. The crude hydrochloride of bis-(1,2-dimethylphenyl)-dimethylaminomethylcarbinol precipitated is converted into the base with the aid of ammonia, dissolved in ether and the pure hydrochloride is precipitated with ethereal hydrochloric acid.

## EXAMPLE X

*Bis-(1,4-dimethylphenyl)-dimethylaminomethylcarbinol*

There are added 20 grams 1,4-dimethylphenyldimethylaminomethylketone in 50 ccm. of absolute ether to a Grignard solution of 50 grams 2-brom-p-xylene, 6.5 grams magnesium and 200 ccm. absolute ether. After the mixture has been heated under reflux for several more hours for the completion of the reaction, the reaction product is worked up as described above.

## EXAMPLE XI

*Phenyl-1.4-dimethylphenyl-dimethylamino-methylcarbinol*

A solution of 20 grams dimethylaminoacetophenone in 50 ccm. ether is added in similar manner to a Grignard solution of 50 grams 2-brom-p-xylene, 6.5 grams magnesium and 200 ccm. absolute ether. After pouring the reaction product into ice and treating with hydrochloric acid, an ethereal solution of phenyl-1.4-dimethylphenyl-dimethylaminomethylcarbinol is obtained by the addition of ammonia and shaking up with ether. The hydrochloride of this compound is obtained by precipitation with ethereal hydrochloric acid and thereupon recrystallizing.

Another method of preparing dialkylaminoalkyl aryl ketones, which are intermediate products in the preparation of the medicaments of the present invention, is to cause aryl magnesium halides to react with dialkylamino-acid amides. The most convenient method of working is to use from 2 to 2½ moles of the aryl-magnesium compound to 1 mole of the dialkyl-acid amide.

## EXAMPLE XII

*Diethylaminoacetophenone*

37 grams of diethylaminodiethylacetamide in 100 ccm. of absolute ether are added gradually to a Grignard solution prepared from 80 grams of brom-benzene, 12.4 grams of magnesium and 200 ccm. of absolute ether. The reaction product is boiled for 1 hour under the reflux condenser for the completion of the reaction, poured on to ice after cooling, and the precipitated basic magnesium bromide is dissolved in hydrochloric acid. The oily, yellow-tinged diethylaminoacetophenone precipitated by treatment with ammonia is dissolved in ether, dried with potash and distilled in vacuo after removal of the ether. The yield amounts to 29 grams of diethylamino-acetophenone=76% of theory.

## EXAMPLE XIII

*Dimethylaminoacetophenone from dimethyl-amtinodiethylacetamide*

A Grignard solution is prepared from 150 grams of brom-benzene, 23 grams mg and 400 ccm. of absolute ether and to same 60 grams of dimethylaminodiethylacetamide in 200 ccm. of ether are added. After heating for one hour on the water bath the reaction product is treated with ice and hydrochloric acid, the base is precipitated with ammonia dissolved in ether and distilled in vacuo after removal of the ether. Yield: 46 grams of dimethylaminoacetophenone=74% of theory.

## EXAMPLE XIV

*Dimethylaminomethyl-1.3-dimethyl-phenylketone*

40 grams of dimethylaminodimethylacetamide in 150 ccm. of absolute ether are added to a Grignard solution prepared from 150 grams of 1.3-dimethyl-4-brom-benzene, 20 grams of magnesium and 400 ccm. of absolute ether. The reaction is completed by heating for from two to three hours on the water bath. The product of reaction is treated with ice and hydrochloric acid, the dimethylamino-1.3-dimethyl-phenylketone is separated from same with the aid of ammonia, dissolved in ether and after drying with potash is distilled in vacuo. Boiling point 144-146° C. (11-13 mms. Hg). The yield amounts to from 60% to 65% of theory.

## EXAMPLE XV

*α-dimethylaminopropiophenone*

A Grignard solution of 80 grams of from benzene, 12.4 grams of magnesium and 200 ccm. of absolute ether is caused to react with a solution of 30 grams of α-dimethylamino dimethylpropionamide in 100 ccm. of absolute ether. The reaction product obtained after heating for two hours on the water bath yields, after treatment with ice and hydrochloric acid and precipitation with ammonia, 26 grams of α-dimethylaminopropiophenone=70% of theory.

Diaryl-aminoalkyl-carbinols are, as such, sparingly soluble or insoluble in water. Hydrochlorides, sulphates and other salts of such compounds with acids which as a rule form readily soluble salts are also very sparingly soluble in the case of the aforesaid compounds.

It has now been found that readily soluble salts of such compounds of the diaryl-aminoalkyl-carbinols are obtained when they are combined with mono- or polyhydroxy-mono-carboxylic acids. Such acids are for example lactic acid, glycolic acid, quinic acid and the like. The manufacture of saline compounds of diaryl-aminoalkyl-carbinols with such acids can be carried out in various ways. It is possible, for example, to introduce the diaryl-aminoalkyl-carbinol into an aqueous solution of the acid and to dissolve it by intensive mixing, or the acid and carbinol can if desired be melted together with the addition of small quantities of water. It is particularly advantageous to dissolve the two components in an organic solvent, for example ether, and to unite the two solutions. The desired saline compound is then in most cases precipitated in a very pure, crystalline form, and can be separated from the solvent. It is not necessary to use in this method of preparation the same solvent for the carbinol as for the acid. It is also possible to use two different solvents, which should as far as possible be capable of mixing together.

## EXAMPLE XVI

*Combination of bis-(1.4-dimethylphenyl)-dimethyl-amino-methylcarbinol with lactic acid*

10 grams of bis-(1.4-dimethylphenyl)-dimethylaminomethylcarbinol and 3.1 grams of lactic acid are dissolved separately in ether and the ether solutions are united. After standing for from 1 to 2 days the crystals separated are separated off by suction filtration. The new compound dissolves to the extent of more than 10% in water, while the hydrochloride of the compound is soluble only up to 0.5%, the sulphate and nitrate up to less than 0.2%.

## EXAMPLE XVII

*Combination of bis-(1.4-dimethylphenyl)-dimethylaminomethylcarbinol with glycolic acid*

10 grams of bis-(1.4-dimethylphenyl)-dimethylaminomethyl-carbinol are added to a concentrated aqueous solution of 2.65 grams of glycolic acid and made to dissolve by intensive stirring and heating on the water bath. The new compound is more than 3% water soluble.

## EXAMPLE XVIII

*Combination of bis-(1.4-dimethylphenyl)-dimethylaminomethylcarbinol with quinic acid*

6.5 grams of quinic acid and 10 grams of bis-(1.4-dimethylphenyl)-dimethylaminomethyl-carbinol are melted together on the water bath with stirring. The solidified crystalline melt dissolves to the extent of more than 5% in water.

## EXAMPLE XIX

*Combination of bis - (1.3-dimethylphenyl) - dimethylaminomethyl-carbinol with lactic acid*

10 grams of bis-(1.3-dimethylphenyl)-dimethylaminomethylcarbinol are dissolved in ether and shaken up with an aqueous lactic acid solution which contains 3.5 grams of pure acid. In this way solutions of more than 20% strength can be made. The hydrochloride of the amino-alcohol is only about 0.6% soluble.

## EXAMPLE XX

*Combination of bis-(p-methylphenyl)-dimethylaminomethyl-carbinol with lactic acid*

10 grams of bis-(p-methylphenyl)-dimethylaminoethylcarbinol and 3.35 grams of lactic acid are dissolved separately in ether and the solutions are combined. The new compound at first separates in an oily state, and can be made to crystallise only with difficulty. In this manner solutions of 50% strength can be made, whereas for example the hydrochloride is soluble only to the extent of 2½%.

A particular advantage of the medicaments of the present invention is that when used on an animal organism they have desirable subsidiary actions, for example many have at the same time a superficial anaesthetic action and the effect of relieving swelling on inflamed mucous membranes. In some cases they possess only one of the two subsidiary actions. The compounds can be applied as such or in the form of their salts, for example as a hydrochloride, benzoate or the like. In this way it is possible to use almost all types of solvent or dispersive agents and to maintain at all times the most favourable hydrogen-ion concentration.

Most of these compounds are in addition non-poisonous, in the quantity required to be used, to the animal organism and are non-irritating even to sensitive mucous membranes.

A few examples will explain this:

An aqueous solution of dimethylaminomethyl-diphenylcarbinol hydrochloride of 2% strength destroys diphtheria bacteria in vitro in 30 minutes. When tested on a rabbit's eye by the bristle method it has a superficial anaesthetic action which is almost equal to that of a solution, also of 2% strength, of cocaine hydrochloricum. In the continuous test, also on a rabbit's eye, even with a 10% solution it was not possible to discover any irritating action.

When a 2% solution is applied to inflamed mucous membranes, distinct relief of the swelling and loss of colour are discernible even after a few minutes. A 2% aqueous solution of dimethylaminomethyl - di - p-tolyl-carbinol hydrochloride kills diphtheria bacteria, in

Vitro .....	in 5 minutes
<i>B. coli</i> .....	in 5 minutes
and	
<i>B. streptococci</i> .....	in 5 minutes

The same solution possesses a surface anaesthetic action approximately four times as strong as that of the first-mentioned compound.

## EXAMPLE XXI

A mouthwash and gargle capable of direct use is obtained by dissolving 5 grams of dimethylaminomethyl-di-2.4-dimethylphenyl-carbinol hydrochloride in 1 litre of water.

## EXAMPLE XXII

*Antiseptic dental tincture*

Spirit (of 90%) 80, tinctura myrrhae 20 and dimethylaminomethyl-di-p-tolyl-carbinol hydrochloride 5. In order to improve the taste suitable substances, for example menthol or ethereal oils, can be added.

## EXAMPLE XXIII

*Mouthwash tablets*

A basic tablet material preferably consisting of sodium chloride is allowed to absorb a solution of dimethylaminomethyl-diphenyl - carbinol - benzoate in alcohol, which contains flavouring additions of peppermint oil, eucalyptus oil or similar ethereal oils.

## EXAMPLE XXIV

*Antiseptic eyewash*

1 gram dimethylaminomethyl-diphenyl-carbinol hydrochloride. 0.7 gram sodium chloride, aqua destillata ad 100.

## EXAMPLE XXV

*Antiseptic vulnerary ointment*

2% of dimethylaminomethyldiphenyl-carbinol hydrochloride is worked into a base of lanolin ointment.

## EXAMPLE XXVI

For the disinfection of burns the latter are smeared with a 2% solution of dimethylaminomethyl-di-p-tolyl-carbinol in olive oil.

## EXAMPLE XXVII

From a basic soap an antiseptic soap is made in known manner by the addition of 5% of dimethylaminomethyl-di-p-tolyl-carbinol.

## EXAMPLE XXVIII

For the sterilisation of surgical instruments the latter are placed in a 2% aqueous solution of dimethylaminomethyl-di - p - tolyl-carbinol hydrochloride.

## EXAMPLE XXIX

By the addition of 0.2% of dimethylaminomethyl-di-2.4-dimethylphenol - carbinol hydrochloride to a solution of adrenaline it is possible to sterilise the latter and keep it sterilised without the application of heat which is harmful to adrenaline. At the same time the dimethylaminomethyl-di-2.4-dimethylphenyl-carbinol hydrochloride supports the action of the local anaesthetic which may be present in the solution. For some purposes the anaesthetic property of the dimethylaminomethyl-di-2.4-dimethylphenyl-carbinol hydrochloride alone is sufficient.

## EXAMPLE XXX

In order to protect glue or gelatine or solutions of same from attack by bacteria, up to 10% and up to 2% of dimethylaminomethyl-di-p-tolyl-carbinol is added to the former and the latter respectively. If an increased fungicidal action is desired, the salt of a per se fungicidal or disinfecting acid, for example benzoic acid or salicylic acid, is advantageously used, or if desired such salts can be used in addition.

EMIL EIDEBENZ.